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Regulation of the Hypothalamic Precursor Cells by HH/GLI Signaling in Post-Embryonic Zebrafish

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Abstract
The major goals of my research were to characterize the hypothalamic neural progenitors and to understand how Hh/Gli signaling plays a role in regulating cell proliferation in the hypothalamic neurogenic zone. In contrast to mammals, the zebrafish brain has a life-long potential to grow

continuously. Thus, for comparative neurogenesis studies, zebrafish become an indispensible model organism to understand adult neurogenesis and regulatory signaling pathways. Identification of the regulatory mechanisms underlying the controlled cell proliferation in adult zebrafish brain will pave the way to manipulate the healing potential of the mammalian brain. Using immunohistochemistry and in situ hybridization techniques to label known markers for neural stem/ and progenitor cells I have identified three different populations of cells with radial glia (RG) like morphology in the adult zebrafish hypothalamic ventricular zone. In adult zebrafish, cells with RG-like morphology in the ventricular regions are thought to be the neurogenic population.

The first population of cells I identified was positive for the neural stem cell marker NESTIN and showed additional characteristics of neural stem cells. Using a label retention assay we showed that Nestin(+) cells are slow cycling. The second population of RG-like cells was Hh responsive, and expressed markers of neural progenitor/transit amplifier cells. Double labeling experiments reveal that the Hh responsive cells were distinct from the Nestin(+) cells These cells were proliferative and cycled faster compared to *nestin(+)* neural stem cells. The third population of cells with RG morphology in the hypothalamic ventricular zone expressed *shh* ligand, indicating a regulatory role for Hh signaling in the hypothalamic ventricular zone. Down-regulation of Hh signaling at larval and adult stages reduced proliferation in the hypothalamic ventricle, indicating that Hh acts as a positive regulator of proliferation, as in the dorsal brain. According to our working model, *nestin(+)* cells are slow cycling, and/or quiescent neural stem cell population in the hypothalamic ventricular zone, whereas Hh responsive cells are the fast cycling transit amplifier cells which proliferate and give rise to new neurons and glia in the adult. My comprehensive analysis of the neural stem/progenitors in the adult zebrafish hypothalamic ventricular zone provides a starting point for the continued study of the mammalian hypothalamic ventricular zone. This study also demonstrates Hh signaling functions as a positive regulator of cell proliferation in the post-embryonic zebrafish hypothalamus consistent with its role in the dorsal brain. (Abstract shortened by UMI.)